REMARKS

Claims 54 and 57 are pending in this application. No claims have been amended. No claims have been cancelled. No new claims have been added.

Claims 54 and 57 have also been rejected under 35 U.S.C. § 112, first paragraph, it being the Examiner's position that the specification does not reasonably provide enablement for R' and R" of formula I coming together to form all of the heterocyclic rings claimed, R_1 and R_2 of formulas I and II coming together to form an oxadiazole, and the R' and R'' substituents of R_9 of the compounds of formula II coming together to form heterocycle, the heterocycle being optionally substituted with halogen, cyano, NO_2 or lactone. Applicants submit that this rejection is not well founded and should be withdrawn as detailed below.

Applicants are not required to specifically teach what is already well known by those skilled in the art. As pointed out in applicants previous response, the specification cites US Patent No. 4,777,167 which describes R' and R" coming together to form piperidino and pyrrolidino. Other prior art shows, for example, morpholino (Sincar, I. et al., *Journal of Medicinal Chemistry*, 1991, 34, 2248-60); thiomorpholino (US Patent No. 4,618,607); and piperazino (US Patent No. 5,034,395). In view of the specific teachings of the present specification and the general level of skill in the art as exemplified by the above-cited references, a skilled person would readily know how to make compounds wherein R' and R" of formula I come together to form the heterocyclic rings recited in the claims.

As to the Examiner's second objection, the oxadiazole compounds can be easily prepared by using the appropriate aldehyde (aldehyde 1f of scheme II) and following reaction scheme II. The use of this aldehyde for making dihydropyridines and the preparation of this oxadiazole-fused benzaldehyde is well documented in the art. See, for example, Leonardi, A., et al., *European Journal of Medicinal Chemistry*, 1998, 33, 399-420; Gasco, A. M., et al., *European Journal of Medicinal Chemistry*, 1996, 31, 3-10; CH 661270. Aldehyde If is also commercially available from MicroChemistry Building Blocks, Order No. mch-bb 2391.

With regard to the Examiner's third objection, applicants once again point out that the claims do not state that the R' and R" substituents on R_9 of the compounds of Formula II come together to form a ring, as suggested by the Examiner. Accordingly, applicants do not understand the basis of this rejection and request that it be withdrawn.

Claims 54 and 57 have also been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants maintain that this rejection is not well founded as discussed below.

The disclosure fully enables those skilled in the art to practice the claimed methods. The use of dihydropyridine-type calcium channel blockers in treating disorders such as hypersensitivity, allergy, asthma and bronchospasm is well-known in the art, as established by the art already of record in this application. It is further noted that because the compounds administered according to the claimed method of treatment are short acting they exert their effects locally. Thus, these compounds, when administered locally to the lungs, are particularly effective for treating the enumerated disorders. The specification at, for example, page 13, lines 12-24, discloses a number of formulations for local administration of these compounds to the lungs via inhalation, including a solution intended for administration by metered dose inhale, or in a form suitable for a dry powder inhaler or insufflator. Typically, administration via inhalation is accomplished by delivering the specified compounds in the form of an aerosol spray from a pressurized container using a suitable propellant and a valve to deliver a metered dose, as is pointed out in the specification and as is well-known in the art.

The Examiner makes comparisons among several of the disclosed compounds to support the objection that the level of predictability in the art is low, arguing that there is a large variation in nitrendipine binding activity with small changes in structure. Applicants submit that the comparisons drawn by the Examiner among the cited compounds are not correct. Compound 1 is a racemic mixture of compounds that has an IC50 of 0.074 μM. When the mixture of enantiomers is resolved, which is explained in detail on pages 23-24, Example 1, compounds 2 and 3 are provided. Compound 2 is the active enantiomer with an IC50 of 0.043 μM and compound 3 is the less active enantiomer with an IC50 of 0.160 μM. Compound 6 is also a racemic mixture of compounds. Therefore, it should properly be compared to compound 1, not to the less active enantiomer, compound 3, as the Examiner has done. Thus, the comparisons among compounds drawn by the Examiner do not support the contention that art is highly unpredictable.

In view of the scope of the disclosure and the level of skill in the art with respect to the use of dihydropyridine-type calcium channel blockers, applicants submit that method of

treatment claims 54 and 57 are fully enabled. Accordingly, applicants request that the rejection of claims 54 and 57 under 35 U.S.C. § 112, first paragraph, be withdrawn and that a Notice of Allowance with respect to these claims be issued at the earliest possible date.

Applicants do not believe that any fees are required in connection with the filing of this Response; however, should any fees be necessary please charge Deposit Account No. 10-0750/ORT-1477/JSK.

Should the Examiner have any questions regarding this Response, please contact the undersigned attorney at the telephone number listed.

Respectfully submitted,

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